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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/187,693	11/05/1998	AYA JAKOBOVITS	4.20-CIP2	3392

7590 12/18/2001

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EXAMINER	
HUYNH, PHUONG N	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 12/18/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Offic Action Summary	Applicati n No.	Applicant(s)	
	09/187,693	JAKOBOVITS ET AL.	
	Examiner	Art Unit	
	" Neon" Phuong Huynh	1644	

-- The MAILING DATE of this communicati n appears on the c ver sheet with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *5/28/99; 11/7/00; 4/10/01* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 1-7 are pending and are being acted upon in this Office Action.

2. The request to amend the Drawings to correct SEQ ID NO, filed 11/17/00, is acknowledged. However, the Patent and Trademark Office no longer makes drawing changes and that it is applicant's responsibility to ensure that the drawings are corrected in accordance with the instructions set forth in the enclosed PTO 948, Notice of Draftsperson's Patent Drawing Review. Appropriate action is required.

3. Applicant should amend the first line of the specification to reflect the status of 09/162,280, filed 9/29/98, and 08/851,362, filed 5/5/97, which is now Pat No. 6,235,883.

4. The disclosure is objected to because of the following informalities: (1) SEQ ID NO: is required on page 48, lines 19 and 21 in the specification; (2) amendment to the **Brief description of the drawings** to include SEQ ID NOS for Figs 1-34, 57-73; (3) the open circle symbol for E7.6.3 in Fig 39 in the brief description is incorrect. It should have been a filled circle; (4) the solid triangle symbol in the brief description of Fig 43 does not match the drawing which is an open triangle; (5) there are extra lines above "myeloma IgG2k, (O)" "violet staining", and "average volume" on page 16, lines 5-6 and line 10; (6) the filled triangle symbol in the brief description of Fig 44 does not match with the open triangle in the Fig 44. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

5. Claim 2 is object to because "phosporylation" is misspelled.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enable only for antibody E7.6.3 having amino acid sequence of SEQ ID NO: 53 (See page 38, line 9-10 and Fig. 33) wherein said antibody binds to the human epidermal growth factor receptor, inhibits tyrosine phosphorylation of the EGF receptor (See Fig 46; page 78-80), is internalized with EGF receptor, inhibits the degradation of EGFR, inhibits EGF induced degradation of EGF receptor (Figs 81-83 and page 92 bridging page 92 and page 95), protects threonin phosphorylation of a 63 KD protein (Fig. 84B and page 93), inhibits VEGF production by A431 tumor cells and ECV304 endothelial cells by 50% and 40%, respectively (page 96, Table II on page 97, in particular) for inhibiting the growth of EGFR positive tumor cells in mice, does not reasonably provide enablement for antibody that binds to *any* EGFR having the functions mentioned above for treating any cancer. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of antibody broadly encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only five humanized antibodies produced by hybridoma E1.1, E2.4, E2.5, E2.11 and E7.6.3 that bind to the human EGF receptor. However, only one antibody produced by hybridoma E7.6.3 has the following functions such as inhibits tyrosine phosphorylation of the EGF receptor (See Fig 46; page 78-80), is internalized with EGF receptor, inhibits the degradation of EGFR, inhibits EGF induced degradation of EGF receptor (Figs 81-83 and page 92 bridging page 92 and page 95), protects threonin phosphorylation of a 63 KD protein (Fig. 84B and page 93), inhibits VEGF production by A431 tumor cells and ECV304 endothelial cells by 50% and 40%, respectively (page 96, Table II on page 97, in particular) for inhibiting the growth of EGFR positive cell such as A431 cells.

The specification does not provide any guidance as how to make and use *any* antibody that binds to *any* EGFR having the functional characteristics mentioned above and capable of inhibiting the growth of any tumor cells in vivo. Given the indefinite number of antibody encompassed by the claims, there are insufficient guidance and working examples in the specification that all undisclosed antibodies have the same functional characteristics and capable of inhibiting every type of tumor such as EGFR negative tumor in vivo. There is insufficient information regarding to the epitope to which the antibody binds and whether the binding specificity is sequential or conformational dependent.

Reins *et al* teach that the tertiary structure, conformation as well as the primary structure of the EGFR are important in determining the specificity of EGFR antibodies (See entire document, Characterization of anti-EGFR mab on page 239 and Inhibition of Cell growth, in particular). As evidence on page 91 of the specification, not all anti-EGFR antibodies inhibit the growth of any tumor and not all tumor cells express EGF receptor. Given the indefinite number of antibody, it is unpredictable which undisclosed antibody would have all the functional characteristics and will be useful for inhibiting tumor in vivo.

For these reasons, the specification as filed fails to enable one skill in the art to practice the invention without undue amount of experimentation. As such, further research would be required to practice the claimed invention.

8. Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification discloses only five antibodies produced by hybridoma E1.1, E2.4, E2.5, E2.11 and E7.6.3 that bind to the human EGF receptor. However, only E7.6.3 antibody has demonstrated the following functions such as inhibits tyrosine phosphorylation of the EGF receptor (See Fig 46; page 78-80), is internalized with EGF receptor, inhibits the degradation of EGFR, inhibits EGF induced degradation of EGF receptor (Figs 81-83 and page 92 bridging page 92 and page 95), protects threonin phosphorylation of a 63 KD protein of the EGFR (Fig. 84B and page 93), inhibits the growth of tumor (A431 cells) in vitro, and inhibits VEGF production by ECV304 endothelial cells (page 96, Table II on page 97, in particular).

There is insufficient **written description** about the structure associated with function of *any* antibody mentioned above for treating *any* tumor. Given the lack of a written description of

any additional representative species of antibody that have the functional characteristics such as the ones recited in the claims, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. See *University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claim 6 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "tumor cells" as recited in claim 6 lacks antecedent base in the base claim 4 because the specification discloses that ECV304 cells are endothelial cells (See page 95, line 8 of the specification).

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 1-7 are rejected under 35 U.S.C. 102(b) as being anticipated by Reins *et al* (J. Cellular Biochemistry 51: 236-248; 1993, PTO 892).

Reins *et al* teach an antibody such as mab 5-D43 that binds to epidermal growth factor receptor, inhibits tyrosine phosphorylation of EGF receptor (EGF-r) and is readily internalized upon binding to EGFR (See page 239, column 2, Results, page 240, column 2, Fig 1, in particular). While the reference is silent that the reference antibody has the functional properties of inhibiting the degradation of EGF-r, inhibiting the EGF induced degradation of EGF-r, protects threonine phosphorylation of EGF-r, protects threonine phosphorylation of a 63 KD protein, inhbiting VEGF production by tumor cells by greater than 50% and inhibiting VEGF production

by endothelial cells by greater than 40% wherein the tumor cells are A431 or ECV304 cells, the reference antibody has the specificity of the claimed antibody and the functional properties would be an inherent property of said antibody. Therefore the claimed antibody appears to be the same as the prior art antibody. Since the Patent Office does not have the facilities for examining and comparing the antibodies of the instant invention to those of the prior art, the burden is on applicant to show that the prior art antibody is different from the claimed antibody. See In re Best, 562 F.2d 1252, 195 USPQ 430(CCPA 1977). Thus, the reference teachings anticipate the claimed invention.

13. Claims 1-7 are rejected under 35 U.S.C. 102(b) as being anticipated by Defize *et al* (J Cell Biology 109(5): 2495-507; Nov 1989, PTO 892).

Defize *et al* teach an antibody that binds to epidermal growth factor receptor such as mAb 2E9 that protects threonine phosphorylation of the EGF receptor (See page 2499, Fig 3C, Table 1, in particular). While the reference is silent that the reference antibody has the property of that recited in claims 1 and 3-7, the molecular weight of this phosphorylated protein to which the reference antibody phosphorylated and the functional properties are the inherent property of the reference antibody. Therefore the claimed antibody appears to be the same as the prior art antibody. Since the Patent Office does not have the facilities for examining and comparing the antibodies of the instant invention to those of the prior art, the burden is on applicant to show that the prior art antibody is different from the claimed antibody. See In re Best, 562 F.2d 1252, 195 USPQ 430(CCPA 1977). Thus, the reference teachings anticipate the claimed invention.

14. Claims 1-7 are rejected under 35 U.S.C. 102(b) as being anticipated by Petit *et al* (Am J Pathol 15(6):1523-30; Dec 1997, PTO 892).

Petit *et al* teach an antibody such as C225 that binds to the epidermal growth factor receptor and inhibits VEGF production in A431 cells. The decrease in VEGF production leads to a significantly reduction in tumor blood vessel counts as a consequence of reduction in endothelial cell proliferation (angiogenesis) (See abstract, in particular). While the reference is silent that the reference antibody has the property of that recited in claims 1-3 and 7, the extend of inhibition of VEGF production such as greater than 50% or 40% and the functional properties are the inherent property of of the reference antibody. Therefore the claimed antibody appears to be the same as the prior art antibody. Since the Patent Office does not have the facilities for

examining and comparing the antibodies of the instant invention to those of the prior art, the burden is on applicant to show that the prior art antibody is different from the claimed antibody. See In re Best, 562 F.2d 1252, 195 USPQ 430(CCPA 1977). Thus, the reference teachings anticipate the claimed invention.

15. Claims 1-7 are rejected under 35 U.S.C. 102(b) as being anticipated by US Pat No 4,943,533, PTO 892).

The '533 patent teaches antibodies such as 579, 455, 225, 528, 579 and 455 that bind to epidermal growth factor receptor (See column 3-10 and claims of '533, in particular). While the reference is silent that the reference antibodies have the property of that recited in claims 1-7, the reference antibodies have the specificity of the claimed antibody and the functional properties of the reference antibodies would be an inherent property of said antibodies. Therefore the claimed antibody appears to be the same as the prior art antibody. Since the Patent Office does not have the facilities for examining and comparing the antibodies of the instant invention to those of the prior art, the burden is on applicant to show that the prior art antibody is different from the claimed antibody. See In re Best, 562 F.2d 1252, 195 USPQ 430(CCPA 1977). Thus, the reference teachings anticipate the claimed invention.

16. No claim is allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

18. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

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Patent Examiner
Technology Center 1600
December 17, 2001

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